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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SLOBODYANSKY, ELIZABETH	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/905,173	SHORT ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-55 and 93-104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-55, 93-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9/15/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed September 15, 2003 amending the specification to correct clerical errors, amending claims 42, 43, 55, 93, 94 and adding claims 95-104 has been entered. It is noted that the amendment indicated the paragraph [0220] as on page 31 while it is on page 53. A note was made in the file to indicate the correct location of the paragraph [0220] as on page 53.

Claims 42-55 and 93-104 are pending and under consideration.

Specification

The disclosure is objected to because of the following:

On pages 74 and 75 Applicants recite "Histadine-phosphate Aminotransferase" where it appears Histidinol phosphate aminotransferase is intended (emphasis added).

Appropriate correction is required.

Claim Objections

Claims 93-104 are objected to because of the following: the independent claims 93 and 95 recite "transaminase" and "aminotransferase". While these terms mean the same activities, the use of a single term in a claim is preferred. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-55 and 93-104 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 42 is drawn to a method of generating a variant nucleic acid encoding a polypeptide having a transaminase activity comprising modifying, deleting or adding one or more nucleotides in a nucleic acid encoding SEQ ID NO:31, SEQ ID NO:23 and sequences complementary thereto. Claims 93 and 95 drawn to a method of generating a variant nucleic acid encoding a polypeptide having a transaminase activity comprising modifying, deleting or adding one or more nucleotides in a nucleic acid encoding an aminotransferase activity and having at least 50% identity to SEQ ID NO:31, 50% identity to SEQ ID NO:23 or sequences complementary thereto. Since the number of possible modifications is not limited, the claims are drawn to a method of generating a variant nucleic acid of an unknown structure encoding a transaminase. Claim 104 depends from claim 95 and is limiting to nucleic acid encoding a histidinol phosphatase aminotransferase activity.

Thus, this part of the claims is directed to a genus of nucleic acid molecules encoding any transaminase or histidinol phosphatase aminotransferase from any source both naturally-occurring and man made. The specification teaches the structure of only a single representative species of such nucleic acids, SEQ ID NO:23. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding a transaminase.

Claim 42 further recites sequences comprising 30 consecutive nucleotides of a nucleic acid encoding SEQ ID NO:31, SEQ ID NO:23, or sequences complementary thereto. 30 nucleotides represent about 3% of the structure of SEQ ID NO:23 that is 1065 nucleotides long encoding 354 amino acids of SEQ ID NO:31. The recited structural feature of the genus (i.e., comprise a fragment of 30 nucleotides of SEQ ID NO:23 or a sequence encoding SEQ ID NO:31) does not constitute a substantial potion of the genus as the remainder of the structure of a polypeptide with transaminase activity is completely undefined. Fragments consisting of 30 nucleotides of SEQ ID NO:23 are highly unlikely to encode transaminase activity and the specification does not define the remaining structural features necessary for members of the genus to be selected.

Claims 93 and 95 recite sequences comprising 30 consecutive nucleotides of a nucleic acid encoding an aminotransferase activity and having 60% identity to SEQ ID

NO:31, or 60% identity to SEQ ID NO:23, or sequences complementary thereto. Similarly, the issues discussed in the preceding paragraph are applicable hereto.

Furthermore, the terms "aminotransferase" or "transaminase" encompass diverse class of enzymes having different substrate and stereo specificity with regard to the amino group donor and acceptor.

The specification does not disclose identifying characteristics which would allow to distinguish an aminotransferase of a defined donor-acceptor and stereo specificity from another aminotransferase specific for a different donor-acceptor pair.

The specification teaches the structure of only a single representative species of such nucleic acids, i.e., that of SEQ ID NO:23 encoding histidinol phosphate aminotransferase (page 74). Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties and/or fails to describe the correlation between structure and function common to all members of the genus. Given this lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims not specifically discussed in this rejection are rejected as dependent from a rejected base claim.

Claims 42-55 and 95-104 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of generating a variant transaminase comprising creating a library of variants of SEQ ID NO: 23 or a sequence encoding SEQ ID NO:31 by modifying (i.e., adding, deleting or substituting) one or more nucleotides of SEQ ID NO: 23, expressing said modified sequences, screening the proteins produced from said modified sequences for transaminase activity and selecting a variant sequence which encodes a protein having transaminase activity, does not reasonably provide enablement for methods of generating variants of SEQ ID NO:23 or variants thereof as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 42-55 and 95-104 are so broad as to encompass methods of making any variant of SEQ ID NO:23. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the

proteins' structure relates to its function. While recombinant and mutagenesis techniques are known, the number of modifications that can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass methods of generating variants of the nucleic acids of SEQ ID NO:23 or encoding SEQ ID NO:31 or variants thereof because one of skill in the art would not know how to use the vast majority of the products of the claimed methods as the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting transaminase activity; (B) the general tolerance of transaminase genes to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including methods of making any variant of SEQ ID NO:23 or encoding SEQ ID NO:31 as the specification does not teach what one would use the

vast numbers of variants which encode proteins lacking any transaminase activity and it is not predictable which modifications will lead to variants encoding active transaminase and will be the substrate and/or stereo specificity of said transaminase. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of methods leading to genes having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 93 and 94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of generating a variant transaminase comprising creating a library of variants of SEQ ID NO: 23 or a nucleic acid encoding SEQ ID NO:31 by modifying (i.e., adding, deleting or substituting) one or more nucleotides of SEQ ID NO: 23 or a nucleic acid encoding SEQ ID NO:31, expressing said modified sequences, screening the proteins produced from said modified sequences for transaminase activity and selecting a variant sequence which encodes a protein having transaminase activity, does not reasonably provide enablement for methods of generating a variant transaminase comprising modifying (i.e., adding, deleting or substituting) one or more nucleotides of SEQ ID NO: 23 or a nucleic acid

encoding SEQ ID NO:31. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 93 and 94 are so broad as to encompass methods of generating a variant transaminase comprising modifying (i.e., adding, deleting or substituting) one or more nucleotides of SEQ ID NO: 23 or a nucleic acid encoding SEQ ID NO:31. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only one transaminase that is histidinol phosphate aminotransferase of SEQ ID NO:31.

While recombinant and mutagenesis techniques are known, there is no expectation in the art that any and all modifications of a sequence can be made without affecting the activity of the encoded protein as required by Claims 93 and 94, and the

positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. As such the skilled artisan would not expect the claimed methods to result in transaminase at all absent a step of screening a group of variant sequences for those which encode proteins which have catalytic activity. Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including methods of generating a variant transaminase comprising modifying (i.e., adding, deleting or substituting) one or more nucleotides of SEQ ID NO:23 or encoding SEQ ID NO:31.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 42-55 and 96-103 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 42 (claims 43-55 dependent thereon) is confusing in the recitation of "sequences comprising at least 30 consecutive nucleotides thereof, and sequences comprising at least 30 consecutive nucleotides of sequences complementary to a sequence as set forth in SEQ D NO:23 ... " because the term "thereof" already encompasses complementary sequences.

Claims 96-103 depend from claim 95 which recites "a polypeptide" in several instances. Therefore, it is unclear to which of the polypeptides recited in claim 95 the dependent claims 96-103 refer.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 42 and 93 are rejected under 35 U.S.C. 102(b) as being by Henner et al.

Henner et al. teach the nucleotide sequence of *Bacillus subtilis* hisH gene within the trp operon (Figure 1). HisH gene encodes a histidinol phosphate aminotransferase. The sequence of HisH gene is at least 50% identical to a fragment of least 30 or 100 nucleotides of SEQ ID NO:23. Henner et al. teach the use of integrative plasmids to produce variant hisH gene with deletions and insertions (Figure 2, Table 1).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 42-55, 93 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henner et al. in view of Short (US Patent 5,939,250).

Claims 42 and 93 are included in this 103 rejection to the extent that they clearly encompass the methods with the limitations of claims 43-55 and 94-104, wherein said modifications are introduced by the specifically claimed methods. These particular embodiments of claims 42 and 93 are not anticipated although as discussed above, claims 42 and 93 also embrace embodiments which are anticipated. Thus both the 102 and 103 rejections are proper.

The teachings of Henner et al. are outlined above. Henner et al. do not use the methods of mutagenesis specifically recited in Claims 43-55 and 94 to produce a variant encoding a transaminase.

Short teaches a number of known techniques for directed mutagenesis for the development of variant nucleic acids. Short specifically teaches "error-prone PCR", "shuffling", "oligonucleotide-directed mutagenesis", "assembly PCR", "sexual PCR mutagenesis", "in vivo mutagenesis", "cassette mutagenesis", "recursive ensemble mutagenesis", "exponential ensemble mutagenesis", "site-specific mutagenesis", "gene reassembly", and "gene site saturated mutagenesis".

One of ordinary skill in the art at the time of filing would have been motivated to modify the nucleic acid sequence hisH gene taught by Henner et al. using each of the methods taught by Short, including "error-prone PCR", "shuffling", "oligonucleotide-directed mutagenesis", "assembly PCR", "sexual PCR mutagenesis", "in vivo mutagenesis", "cassette mutagenesis", "recursive ensemble mutagenesis", "exponential ensemble mutagenesis","site-specific mutagenesis", "gene reassembly", "gene site saturated mutagenesis", in order to identify the role of hisH gene in the *Bacillus subtilis trp* operon and metabolism. One of ordinary skill in the art at the time of filing would have a reasonable expectation of success because of the high level of knowledge in the field of nucleic acid mutagenesis and the teachings of Henner et al. who successfully generated a variant of hisH gene using plasmids interrupting the promoter

region thereof. Thus Henner et al. and Short make obvious claims 42-55, 93 and 94 drawn to methods of generating a variant of a nucleic acid encoding a transaminase comprising a sequence homologous to SEQ ID NO: 23 and modifying, deleting or adding one or more nucleotides in said sequence to another nucleotide, wherein the modifications are introduced by error-prone PCR (claims 43,44 and 94), shuffling (claims 43, 45 and 94), oligonucleotide-directed mutagenesis (claims 43, 46 and 94), assembly PCR (claims 43, 47 and 94), sexual PCR mutagenesis (claims 43, 48 and 94), in vivo mutagenesis (claims 43, 49 and 94), cassette mutagenesis (claims 43, 50 and 94), recursive ensemble mutagenesis (claims 43, 51 and 94), exponential ensemble mutagenesis (claims 43, 52 and 94), site-specific mutagenesis (claims 43, 53 and 94), gene reassembly (claims 43, 54 and 94), or gene site saturated mutagenesis (claims 43, 55 and 94).

Response to Arguments

Applicant's arguments filed September 15, 2003 have been fully considered but they are not persuasive.

With regard to the election of Group IV, claims 42-55 and a polynucleotide encoding SEQ ID NO:31, with traverse made March 25, 2003 (Paper No. 14), Applicants argue that "the Patent Office should reconsider and allow the rejoinder of nucleotide groups A, B, C, D, F, and J, all transaminases originally derived from the

organism *Aquifex*" (Remarks, page 14, first two paragraphs). This is incorrect because some sequences derived from *Ammonifex* and *Pyrobacullum*. Additional arguments are given in the Office action mailed June 17, 2003.

With regard to the 112, 1st paragraph, written description rejection, Applicants argue that "In example 14 of the guidelines (a copy of which is attached as Exhibit A), a claim reciting variants claimed by sequence identity to a sequence is sought (specifically, "A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A-B). In the example, the specification is described as providing SEQ ID NO:3 and a function for the protein. The specification contemplates, but does not exemplify variants of SEQ ID NO:3 that have substitutions, deletions, insertions and additions. ... the analysis of example 14 states that procedures for making variants (which have 95% sequence identity) are conventional in the art" (Remarks, page 16). This is not persuasive because the example in the Guidelines is different from the instant case. First, the claimed variants must be 95% identical to the sequence of the protein that exhibits the requisite catalytic activity. Therefore, said variants are described by structure. In the instant case, as explained above, the claimed polypeptide may have a very low or no homology to a protein exhibiting catalytic activity. Therefore, in the instant case there is insufficient structural limitations. Second, in the example the activity is known. Instead, in the instant case, the reaction that is catalyzed is unknown because transaminases catalyze

numerous different reactions. Applicants further argue that "the requirements for written description of a genus of nucleic acids set forth in University of California v. Eli Lilly & Co., 43 USPQ2d 1398 (Fed. Cir. 1997). In Lilly, the Court stated that, "[a] description of a genus of cDNA may be achieved by means of a recitation of a representative number of cDNAs ... *or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.*" (emphasis added) Lilly, 43USPQ2d at 1406" page 17). This is not agreed with because as explained above in the instant case, the structural features common to the members of the genus do not constitute a substantial portion of the genus as the remainder of the structure of a polypeptide with transaminase activity is completely undefined. Fragments consisting of 30 nucleotides of SEQ ID NO:23 are highly unlikely to encode transaminase activity and the specification does not define the remaining structural features necessary for members of the genus to be selected.

The previous 112, 2nd paragraph, rejection is moot in view of the amendment.

With regard to the 102(b) and 103 rejections, Applicants argue that "The instant amendment addresses this issue" and "Henner is further defective in that it does not teach the sequences modified in the claimed methods (pages 19-20). This is not persuasive for the reasons explained in the rejections above.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner

December 10, 2003